The Current State of Peritoneal Dialysis

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Number of Words in Abstract: 242

Number of Words in Text: 3779

Number of Tables: 2

Number of Figures: 5

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Abstract

It took almost 60 years for peritoneal dialysis (PD) to be used widely for the long-term treatment of end-stage renal disease. Technical innovations resulted in a significant reduction in therapy-related complications, allowing patients to be maintained on PD for longer periods of time. More recently, there has also been a greater decrease in mortality for patients treated with PD compared to in-center hemodialysis such that the two modalities now provide equivalent patient survival. In parallel, changes in public policy have spurred an unprecedented expansion in the use of PD in several parts of the world. Our understanding of the molecular mechanisms involved in solute and water transport across the peritoneum has expanded leading to the identification of potential therapeutic targets for improving efficiency of PD. The pathobiology of structural and functional changes in the peritoneum with long-term PD has also been clarified providing new targets for intervention. As with hemodialysis, almost half of all deaths on PD occur because of cardiovascular events and there is great interest in identifying modality-specific factors contributing to the high risk for cardiovascular events. Tremendous progress has been made in developing interventions that substantially reduce the risk of PD-related peritonitis. Yet, the gains have been unequal primarily because of unequal application of knowledge from research into clinical practice. The work to date has further highlighted the areas in need for innovation as we continue to strive to improve the health and outcomes of patients treated with PD.

Key Words: peritoneum; end-stage renal disease; peritoneal solute transfer rate; fibrosis; ultrafiltration failure; cardiovascular disease; metabolic; peritonitis; mortality

The first attempt to use the human peritoneum to dialyze uremic retention solutes was made almost one hundred years ago[1]. Over the next five decades, the therapy gradually evolved with an expansion in our understanding of solute and water kinetics that allowed for successful application of this mode of dialysis to acute kidney injury and end-stage renal disease (ESRD)[2-10]. This, in addition to the development of indwelling catheter that provided access to peritoneal cavity at will and standardization of the composition of dextrose-based dialysate culminated in the introduction of continuous ambulatory PD in 1976 (Figure 1)[11-13]. This was followed by changes in connectology to reduce the risk of infections, the introduction of volumetric cyclers, and several alternatives to conventional glucose-based PD solutions[13-16]. In this review, we highlight the major developments in the application of PD for the treatment of ESRD.

Utilization and Outcomes with Peritoneal Dialysis

The early experience with PD raised numerous concerns whether the therapy was a viable alternative to in-center hemodialysis for the long-term treatment of ESRD. These included but were not limited to high risks of infections, inadequate clearance of small solutes, and deterioration of peritoneal health resulting in ultrafiltration failure, which together led to shorter time on therapy and higher risk for death compared to in-center hemodialysis[13, 17-19]. This led a leading nephrologist to retort in the 1980s that PD is a "second-class therapy for second-class patients by second-class doctors". In part driven by these concerns, starting from the mid-1990s the proportion of patients with ESRD treated with PD progressively declined in many parts of the world[20, 21].

Yet, the greatest improvements in the clinical application of PD occurred at the same time as a progressively smaller proportion of patients were utilizing the therapy. In the decade starting from the mid-1990s, there was a significantly larger reduction in risk for

death for patients starting with PD around the world than for those undergoing in-center hemodialysis (Table 1)[22-29]. As a result, virtually all studies indicate PD and in-center hemodialysis now provide similar short (1- or 2-year) or long-term (up to 5 years) survival (Table 1)[23-25, 29-31]. Furthermore, there has been a significant reduction in risk of patients treated with PD transferring to in-center hemodialysis in the United States indicating a lower risk of therapy-related complications[32]. These improvements have significant implications as they allow patients to receive treatment with a renal replacement therapy best suited to their values, expectations, and lifestyles, and nations the flexibility to incentivize dialysis modalities that allow them to offer cost-effective treatment given increasing budgetary constraints.

Public Policy Changes to Increase PD Utilization

The relative costs of hemodialysis and PD vary around the world{Karopadi, 2013 #1}. In most developing countries and many developing countries societal costs with PD are lower providing impetus to these jurisdictions to enact public policy that promotes the use of a cheaper therapy{Karopadi, 2013 #1}. This is important as it has long been recognized that non-medical factors, including reimbursement, are the primary determinants of the proportion of ESRD patients treated with PD in any region of the world[33, 34]. With a backdrop provided by recent studies that PD provides equivalent survival to in-center hemodialysis, several countries around the world have introduced changes to increase PD utilization to leverage its lower costs to the health-system[35]. In the United States, an expanded prospective payment system became effective in 2011, which includes the cost of parenteral dialysis-related medications in capitated payments made for each dialysis treatment[36, 37]. Since PD patients require a significantly lower dose of erythropoiesis stimulating agents to achieve any given hemoglobin level, this policy change offers a

significant financial incentive to a greater use of PD[38]. In Thailand, the government adopted a "PD-First" approach in 2008 as part of its universal health coverage scheme, as in Hong Kong, under the aegis of which dialysis services will be paid for only if the patient is treated with PD, given its lower cost[39]. Finally, China has been rapidly expanding access to renal replacement therapy to its population and has a policy that encourages the use of PD without mandating it[35]. Each of these three countries has seen an unprecedented expansion in the use of PD. The growth in the United States has been so rapid (Figures 1 and 2) that the dominant manufacturer was not able to increase the supply of dialysate to meet the increasing demand leading to rationing of solutions in 2014[40]. The shortage has abated but has not been completely eliminated.

Rethinking Care Delivery to Increase Dialysis Treatment Options for Patients

An important barrier to a greater use of PD is that many patients with ESRD are unaware that dialysis can be done at home[41, 42]. Conversely, educating patients about treatment options is associated with a significantly higher use of PD even among patients who start dialysis without prior care with a nephrologist[43, 44]{Rioux, 2011 #2}. Even when practices make comprehensive modality education programs available, many patients start renal replacement therapy with little or no prior care by a nephrologist. These late-referred patients invariably start treatment with in-center hemodialysis with a central venous catheter[45, 46]. Even though "urgent-start" PD has been performed for decades, a growing number of centers around the world have developed these programs both to increase the use of PD and reduce the proportion of patients that start dialysis with a central venous catheter[47-55]. Successful implementation of "urgent-start" PD requires (1) the ability to educate late-referred patients on short notice about treatment options; (2) place PD catheters in a timely manner; and (3) offer intermittent PD in a hospital or dialysis facility up

until the patient can be trained to perform treatments safely at home[56]. A large number of case-series have reported successful implementation of "urgent-start" PD without an increase in incidence of leaks or other therapy-related mechanical complications[47-55].

The elderly or the disabled is another group of patients that have significantly lower use of PD, even though many such patients would prefer treatment at home[57]. Many programs have long used family members to help patients with PD[58]. Several countries have extended this concept to include a visiting nurse to help patients with PD at home[57, 59-62]. Some of these patients require assistance only for a short-period of time[61]. Observational studies suggest that patients undergoing assisted PD have similar rates of bacterial peritonitis as with self-care PD and similar patient-reported outcomes and hospitalization as with in-center hemodialysis[59, 62, 63].

Finally, racial/ethnic minorities in the United States have a significantly lower use of home-based dialysis therapies[64]. It is imperative to further study this to ensure all patients have equal access to all dialysis modalities without regard to their race/ethnicity.

Improved Understanding of Peritoneal Physiology and Pathophysiology

The primary goal of dialysis is to remove water and uremic solutes, and the effectiveness of their removal is an important determinant of outcomes of patients treated with PD[65, 66]. Recent studies have expanded our understanding of solute and water transfer across the peritoneum some of which could be leveraged for increasing the efficiency of PD.

Aquaporins in the Peritoneum

The water channel aquaporin-1 is constitutively expressed in endothelial cells lining peritoneal capillaries[67]. It is a member of a highly conserved family of water channels that are organized as homotetramers, with each monomer containing a central pore that facilitate the movement of water across the lipidic membranes [68]. The deletion of *Aqp1* in

mice results in 70% decrease in solute-free ultrafiltration, 50% decrease in cumulative ultrafiltration, and abolition of sodium sieving[69, 70]. Indeed, glucose is effective as an osmotic agent because of the presence of aquaporin-1 in peritoneal endothelial cells[71]. Investigators are currently examining aquaporin-1 as a therapeutic target to increase ultrafiltration with PD. High-dose dexamethasone increases aquaporin-1 expression in peritoneal capillaries of rodents resulting in enhanced free-water transport and ultrafiltration[72]. Steroids may be efficacious in humans as illustrated by comparing ultrafiltration in patients before and after kidney transplantation[73]. Another potential agent is an arylsulfonamide, AqF026, the first pharmacological agonist of aquaporin-1 that interacts with an intracellular loop involved in the gating of the channel[74]. It enhances aquaporin-mediated water transport and net ultrafiltration in rodents. These two examples give hope for the possibility of developing pharmacologic therapies targeting aquaporin-1 to enhance ultrafiltration with PD.

Intra-peritoneal inflammation

There is increasing evidence that differences in chronic intraperitoneal inflammation, particularly interleukin-6 production by mesothelial and resident cells in the peritoneum, are primarily associated with differences in peritoneal solute transfer rate, which are in turn strongly associated with PD clinical outcomes[65, 66, 75-78]. Consistent with this, genetic variants associated with higher interleukin-6 production are associated with higher peritoneal solute transfer rate[79, 80].

In addition to chronic inflammation, episodes of peritonitis are associated with acute increases in intraperitoneal inflammation resulting in higher peritoneal solute transfer rates and lower ultrafiltration[81]. Studies in rodents suggest that locally released vasoactive substances, particularly nitric oxide, may mediate the increase in peritoneal solute transfer

rate[82-84]. Pharmacological inhibition or genetic deletion of the endothelial nitric oxide synthase significantly attenuates intraperitoneal inflammation in animals with peritonitis and the associated change in peritoneal solute transfer rate and ultrafiltration[83].

These findings point to potential therapeutic targets to be explored in the future to improve PD efficiency.

Structural and Functional Changes over time

Prolonged treatment with PD is associated with structural (fibrosis, angiogenesis, hyalinizing vasculopathy) and functional (increased peritoneal solute transfer rate, ultrafiltration failure) changes[85]. One of the most serious complications of long-term PD is encapsulating peritoneal sclerosis, a rare complication characterized by an exaggerated fibrogenic response of the peritoneum[86, 87]. Studies suggest that peritoneal ultrafiltration capacity decreases prior to the clinical manifestation of encapsulating peritoneal sclerosis[88, 89] and that the primary mechanism is reduction in osmotic conductance (ultrafiltration volume for a given osmotic gradient) that is related to the increased collagen fiber density in the interstitium[86].

The mechanisms of peritoneal fibrosis remain debated. Progressive fibrosis is characterized by the release of growth factors such as TGF-β1, resulting in the accumulation of α-smooth muscle actin myofibroblasts in the peritoneum[85, 90]. Several *in vitro* and *in vivo* studies indicated that myofibroblasts are derived from mesothelial cells through epithelial-mesenchymal-transition[91-94], in which epithelial cells lose their polarity and differentiation, gain migratory and invasive properties, and become pluripotent mesenchymal stem cells that differentiate into fibroblasts. Consistent with studies questioning the role of epithelial-mesenchymal transition in renal fibrosis[95-97], Chen *et al*[98] recently applied lineage-tracing technology in several models of peritoneal fibrosis and showed that submesothelial

fibroblasts – and not mesothelial cells via epithelial-mesenchymal transition - are the major precursors of myofibroblasts.

These improvements in our understanding of the mechanisms involved in changes in the peritoneum with long-term PD hold hope that future therapies may allow us to ameliorate them. As an example, *post-hoc* analysis of a recent randomized controlled trial suggests that patients treated with biocompatible PD solutions may not have the increase in peritoneal solute transfer rate after the first month of therapy as seen with conventional PD solutions[99, 100]. Observational studies have also raised the possibility that inhibitors of renin-angiotensin-aldosterone system may ameliorate change in peritoneal solute transfer capacity over time{Kolesnyk, 2009 #3}; the beneficial effect of these drug classes, however, has not been tested in clinical trials.

Cardiovascular Risk Modification in PD patients

About 40-60% of deaths in PD patients are associated with cardiovascular events[101]; even more can be considered indirectly related if the link between cardiovascular disease, inflammation and frailty leading to debilitation, transfer to hemodialysis, and treatment withdrawal are considered[77, 102-104]. Registry analyses suggest that PD patients may have a higher risk of myocardial infarction compared to hemodialysis[101, 105]. This section is focused on non-conventional cardiovascular risk factors, with emphasis on modification by treatment with PD (Figure 4). A more comprehensive evaluation of evidence of cardiovascular risk factors is included in recently published clinical practice guidelines[106, 107].

Importance of metabolic risk factors and the role of glucose-sparing regimens

The most obvious risk factors exacerbated by PD are metabolic, related to systemic glucose absorption from the dialysate. They include worsening dyslipidemia, insulin resistance and metabolic syndrome, and weight gain[108-114]. Yet, the evidence that they

translate into significantly worse outcomes for PD patients is variable. For example, the greater weight gain with PD compared to hemodialysis is unclear. Patients gain weight after starting PD, and this is closely mirrored by an increase in total cholesterol and fat mass. However, in many circumstances this weight gain reflects catch-up of the pre-dialysis loss [108, 115]. This also happens with hemodialysis and a large study found that the risk of significant weight gain is lower with PD[115]. For patients undergoing maintenance dialysis, the greater nutritional risk is being underweight and in this context additional calories from the dialysate could be advantageous[116, 117]; what is less clear is whether the lower death risk with larger body size consistently observed among patients undergoing hemodialysis is seen with PD[118]. This may be influenced by other regional factors as the risk or benefit of being obese in PD varies between national registries, being harmful in Australasia and neutral or advantageous in the United States and Brazil[115, 119-121].

One potential shortcoming of the registry analyses is the use of body mass index as surrogate for obesity which may under-estimate fat gain in PD patients; the preferred use of waist circumference in defining metabolic syndrome is also hard to validate in PD patients in whom abdominal girth measurements are influenced by intra-abdominal fluid. Equally, measuring insulin resistance in a patient who is never fasting because of continuous glucose absorption presents problems. This may explain the inconsistencies between studies linking metabolic syndrome in PD to worse outcomes[111, 122, 123]. Again the role of treatment modality varies, as new-onset diabetes is less common in Chinese patients treated with PD than hemodialysis, and in either dialysis modality much less than for newly transplanted patients[124, 125]. What at first sight may be an obvious modality-specific risk factor for cardiovascular disease, i.e. systemic glucose absorption, turns out to be much less clear.

Regardless of these inconsistencies, there are now several studies showing that these risk factors are modifiable, although none of the trials are sufficiently powered to address hard endpoints. Glucose sparing solutions have been developed, such as amino-acid and icodextrin. In non-diabetics icodextrin used in the long exchange prevents non-fluid (presumed fat) weight gain and improves insulin resistance[126-128]. In diabetics, including when in combination with amino-acid solutions, icodextrin improves glycemic control and lipid profiles[129-131]. Poor glycemic control is associated with worse outcomes in diabetic PD patients[132, 133].

Given the concern of increased risk of myocardial infarction in PD patients the lack of evidence that statins can reduce this is disappointing[134]. Interestingly a pre-specified subgroup analysis of the SHARP study, the only trial to include PD patients, found a non-significant but potentially important risk reduction suggesting that these patients may be different and worthy of further investigation[135].

Residual Kidney Function

Residual kidney function is strongly associated with better survival in studies of both PD and hemodialysis[136, 137]. In the CANUSA study every 250 ml higher urine volume per day translated into a 36% lower 2-year mortality[136]. Evidence suggests that PD is associated with better preservation of residual kidney function compared to hemodialysis, typical reported rates of loss in clearance per month being 0.25-0.28 and 0.30-0.40 ml/min/1.73m^2, respectively[138-143]; the mechanism is still debated but is likely in part the avoidance of intravascular volume depletion which occurs more frequently with hemodialysis[144]. Cohort studies and controlled trials find that in patients undergoing PD the rate of loss of kidney function could be slowed with avoidance of volume depletion, use of blockers of renin-

angiotensin-aldosterone system, and the use of diuretics (urine volume and sodium loss)[142, 143, 145, 146].

The most studied intervention to maintain residual kidney function is the use of biocompatible solutions. Biocompatible solutions avoid the need for sterilizing glucose at higher pH so limiting the formation of glucose degradation products and thus avoiding their associated toxicity. The balANZ study demonstrated that these solutions delay the time to anuria, and slow the rate of loss of clearance from 0.28 to 0.22 ml/min/1.73m^2/month[147]. Subsequent meta-analyses have confirmed this observation[140, 148].

Volume management

As already alluded to, volume depletion puts residual kidney function at risk but equally volume excess is detrimental. Hypertension in patients healthy enough to be wait-listed for transplant is associated with worse survival and there is a growing body of evidence from bioimpedance data that over-hydration predicts worse survival[149, 150]. In anuric patients the ultrafiltration performance of the peritoneum becomes critical and daily net fluid removal of < 750-1000 ml is associated with higher mortality[151, 152]. There is evidence that automated PD and icodextrin use can improve the risks associated with fast peritoneal solute transfer rate[66, 153, 154].

The fluid status of PD patients is no worse on average than for hemodialysis patients pre-dialysis, but that the distribution of fluid is likely different[144]. Hypoalbuminaemia is more common with PD due to the additional peritoneal protein losses and is a reflection of their largely independent systemic and intraperitoneal inflammatory states[77, 155]. Intravascular plasma volume is typically normal in PD, even when excess fluid associated with hypoalbuminemia is present, indicating it being in the interstitial compartment[156]. This means that normalizing fluid status runs the risk of plasma volume depletion, hypotension,

and faster loss of residual kidney function. A recent trial using bioimpedance to support clinical decision making found that fluid status was very stable in PD patients with residual kidney function whereas the challenge in anuric patients was how to reduce volume status so that extracellular fluid was reduced in parallel with the loss in lean body tissue[157]. The only intervention that achieved this was an increase in glucose prescription. As things stand clinicians need to exercise caution and clinical judgment in setting target weights.

Peritonitis

Peritonitis continues to be a major cause of morbidity and mortality in PD patients globally[101, 158, 159]. Depending on the underlying causative organism, PD-related peritonitis is complicated by relapse in 3-20% (14% overall), catheter removal in 10-88% (22% overall), permanent hemodialysis transfer in 9-74% (18% overall), and death in 0.9-8.6% of cases (2-6% overall)[160-171]. Following a single episode of peritonitis, the risks of death due to infection, cardiovascular disease and dialysis withdrawal are markedly increased in the first month and continue to remain significantly elevated for up to 6 months afterwards[103]. Severe and/or repeated peritonitis episodes may also culminate in sufficient damage that precludes successful PD and, rarely, encapsulating peritoneal sclerosis[172, 173]. The complication imposes a heavy financial burden on the healthcare system with one health economics analysis estimating the average cost of peritonitis-related hospitalization to be of the order of $3100[174]. Finally, concern about the risk of PD peritonitis represents one of the most important patient-related barriers to the greater uptake of PD[175].

Nevertheless, peritonitis is a preventable condition and there is abundant evidence that infection rates around the world have decreased considerably over time[176]. Single center observational studies from different parts of the world, as well as a multi-national national registry studies have reported that the rates of PD-related infections have steadily

decreased over the last 10-20 years[158, 177-182]. Although this reduction has been most apparent for Gram-positive infections, significant reductions have also been reported for Gram-negative peritonitis[158, 177-182]. These reductions have been variously attributed to the use of twin bag disconnection systems, implementation of mupirocin chemoprophylaxis protocols, topical exit site application of gentamicin, co-prescription of nystatin or fluconazole with antibiotic therapy, improved training of PD patients and/or staff, and better identification and targeting of peritonitis risk factors[177, 183-190]. Within Australia, country-wide PD-related peritonitis rates fell significantly by 37% over a 5-year period from 0.62 episodes per patient-year in 2008 to 0.39 episodes per patient-year in 2013 following a concerted, multi-disciplinary and multi-pronged national peritonitis reduction campaign involving quarterly audit and feedback of individual unit peritonitis rates, prioritization of peritonitis prevention trials by the Australasian Kidney Trials Network, updating national clinical practice guidelines on peritonitis, launching peritonitis guideline implementation projects, publishing of a call to action paper, establishment of a PD Academy to provide PD training to junior nephrologists and nursing staff, and development of a Home Dialysis Network to support home dialysis patients (http://homedialysis.org.au/)[191-196].

Despite these improvements, there remains a wide and unacceptable variation in reported rates from different countries, ranging from 0.06 episodes/ year in Taiwan to 1.66 episodes/ year in Israel[197]. Furthermore, up to 20-fold variation in peritonitis rates has been reported between centers within individual countries, such as Australia (Figure 5)[171, 191], Austria[198], Scotland[199], and the United Kingdom[200]. The sources of these variations have not been adequately investigated but may relate to center-related factors, such as unit size, topical antibiotic prophylaxis or PD training practices[158, 189, 198, 199, 201, 202]. A previous national survey found highly variable and generally poor compliance of centers with clinical practice

guidelines for prevention of peritonitis[203]. More recently, an ANZDATA Registry analysis found that the wide variation in peritonitis rates across Australian dialysis centers was decreased by 16% after adjustment for patient characteristics (e.g. demographics, comorbidities), and was reduced by a further 34% after accounting for a limited number of center-level characteristics, such as unit size, proportion of dialysis patients treated with PD, use of anti-fungal chemoprophylaxis, icodextrin use, performance of peritoneal equilibration tests, cycler use and propensity to admit patients with PD-related peritonitis to hospital[204]. This observation suggests that center practices play a dominant role in mediating between-center variation in peritonitis rates. Similarly, unacceptable variations in the outcomes of peritonitis treatment have been significantly associated with observed deviations in practice from clinical practice guidelines[205].

The key message from these studies is that although peritonitis rates are generally improving globally over time, there have been marked and unacceptable variations in peritonitis rates and outcomes between centers in many countries. This variation is explained to a large extent by variation in center practices, with poorer results generally being observed in units that deviate from evidence-based best practice recommendations (and not infrequently from their own unit policies)[205]. Key strategies for correcting this ubiquitous problem in PD include benchmarking of PD center peritonitis rates and outcomes through the establishment of national PD peritonitis registries within each country, alignment of PD practice in each center with clinical practice guidelines, strengthening of clinical governance within each unit and adoption of a whole-of-unit approach to continuous quality improvement, including root cause analysis of all cases of peritonitis within each center to identify areas for improvement[197, 206].

Future Directions

Despite tremendous progress on multiple fronts, patients with end-stage renal disease carry a heavy burden of disease and treatment. We owe to the patients to continue to reconfigure health care delivery to better match dialysis modality to patients' desires, improve the efficiency of therapy without putting a greater burden on patients, reduce cardiovascular risk, and better apply lessons learnt from research in clinical practice (Table 2).

Acknowledgements

Studies mentioned in this review were supported in part by the National Institutes of Health (R01DK99165), Fondation Saint-Luc at UCL, Baxter Extramural Grants, the Fonds National de la Recherche Scientifique, and the NCCR Kidney.CH program (Swiss National Science Foundation).

Potential Conflicts of Interest

Simon Davies has received research funding, speakers honoraria and participated in occasional advisory boards for Baxter Healthcare and Fresenius Medical Care.

David Johnson has previously received consultancy fees, research funds, speakers' honoraria and travel sponsorships from Baxter Healthcare and Fresenius Medical Care.

Rajnish Mehrotra and Olivier Devuyst do not report any potential conflicts of interest.

References:

1. Ganter G: Uber die Beseitigung giftiger Stoffe aus dem Blute durch Dialyse. *Munch Med Wochenschr,* 70**:** 147-1481, 1923.

2. Wear JB, Sisk IR, Trinkle AJ: Peritoneal lavage in the treatment of uremia: an experimental and clinical study. *J Urol,* 39**:** 53-62, 1938.

3. Frank HA, Seligman AM, Fine J: Treatment of uremia after acute renal failure by peritoneal irrigation. *JAMA : the journal of the American Medical Association,* 130**:** 703-705, 1946.

4. Seligman AM, Frank HA, Fine J: Treatment of Experimental Uremia by Means of Peritoneal Irrigation. *The Journal of clinical investigation,* 25**:** 211-219, 1946.

5. Frank HA, Seligman AM, Fine J: Further experiences with peritoneal irrigation for acuter renal failure including a description of modifications in method. *Annals of surgery,* 128**:** 561-608, 1948.

6. Odel HM, Ferris DO, Power MH: Peritoneal lavage as an effective means of extrarenal excretion; a clinical appraisal. *The American journal of medicine,* 9**:** 63-77, 1950.

7. Grollman A, Turner LB, Mc LJ: Intermittent peritoneal lavage in nephrectomized dogs and its application to the human being. *AMA archives of internal medicine,* 87**:** 379-390, 1951.

8. Doolan PD, Murphy WP, Jr., Wiggins RA, Carter NW, Cooper WC, Watten RH, Alpen EL: An evaluation of intermittent peritoneal lavage. *The American journal of medicine,* 26**:** 831-844, 1959.

9. Maxwell MH, Rockney RE, Kleeman CR, Twiss MR: Peritoneal dialysis. 1. Technique and applications. *Journal of the American Medical Association,* 170**:** 917-924, 1959.

10. Boen ST, Mulinari AS, Dillard DH, Scribner BH: Periodic peritoneal dialysis in the management of chronic uremia. *Transactions - American Society for Artificial Internal Organs,* 8**:** 256-262, 1962.

11. Tenckhoff H, Schechter H: A bacteriologically safe peritoneal access device. *Transactions - American Society for Artificial Internal Organs,* 14**:** 181-187, 1968.

12. Popovich RP, Moncrief JW, Decherd JB, Bomar JB, Pyle WK: The definition of a novel portable/wearable equilibrium peritoneal dialysis technique. *Transactions - American Society for Artificial Internal Organs,* 5**:** 484-489, 1976.

13. Oreopoulos DG, Robson M, Izatt S, Clayton S, deVeber GA: A simple and safe technique for continuous ambulatory peritoneal dialysis (CAPD). *Transactions - American Society for Artificial Internal Organs,* 24**:** 484-489, 1978.

14. Maiorca R, Cantaluppi A, Cancarini GC, Scalamogna A, Broccoli R, Graziani G, Brasa S, Ponticelli C: Prospective controlled trial of a Y-connector and disinfectant to prevent peritonitis in continuous ambulatory peritoneal dialysis. *Lancet,* 2**:** 642-644, 1983.

15. Buoncristiani U: Birth and evolution of the "Y" set. *ASAIO J,* 42**:** 8-11, 1996.

16. Diaz-Buxo JA, Farmer CD, Walker PJ, Chandler JT, Holt KL: Continuous cyclic peritoneal dialysis: a preliminary report. *Artificial organs,* 5**:** 157-161, 1981.

17. Ahmad S, Gallagher N, Shen F: Intermittent peritoneal dialysis: status reassessed. *Transactions - American Society for Artificial Internal Organs,* 25**:** 86-89, 1979.

18. Heimburger O, Waniewski J, Werynski A, Tranaeus A, Lindholm B: Peritoneal transport in CAPD patients with permanent loss of ultrafiltration capacity. *Kidney international,* 38**:** 495-506, 1990.

19. Bloembergen WE, Port FK, Mauger EA, Wolfe RA: A comparison of mortality between patients treated with hemodialysis and peritoneal dialysis. *Journal of the American Society of Nephrology : JASN,* 6**:** 177-183, 1995.

20. Mehrotra R: Peritoneal dialysis penetration in the United States: march toward the fringes? *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 26**:** 419-422, 2006.

21. Jain AK, Blake P, Cordy P, Garg AX: Global trends in rates of peritoneal dialysis. *Journal of the American Society of Nephrology : JASN,* 23**:** 533-544, 2012.

22. Mehrotra R, Kermah D, Fried L, Kalantar-Zadeh K, Khawar O, Norris K, Nissenson A: Chronic peritoneal dialysis in the United States: declining utilization despite improving outcomes. *Journal of the American Society of Nephrology : JASN,* 18**:** 2781-2788, 2007.

23. Mehrotra R, Chiu YW, Kalantar-Zadeh K, Bargman J, Vonesh E: Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Archives of internal medicine,* 171**:** 110-118, 2011.

24. Chang YK, Hsu CC, Hwang SJ, Chen PC, Huang CC, Li TC, Sung FC: A comparative assessment of survival between propensity score-matched patients with peritoneal dialysis and hemodialysis in Taiwan. *Medicine,* 91**:** 144-151, 2012.

25. Yeates K, Zhu N, Vonesh E, Trpeski L, Blake P, Fenton S: Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 27**:** 3568-3575, 2012.

26. Heaf JG, Wehberg S: Relative survival of peritoneal dialysis and haemodialysis patients: effect of cohort and mode of dialysis initiation. *PloS one,* 9**:** e90119, 2014.

27. Marshall MR, Polkinghorne KR, Kerr PG, Agar JW, Hawley CM, McDonald SP: Temporal Changes in Mortality Risk by Dialysis Modality in the Australian and New Zealand Dialysis Population. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 66**:** 489-498, 2015.

28. Ryu JH, Kim H, Kim KH, Hann HJ, Ahn HS, Lee S, Kim SJ, Kang DH, Choi KB, Ryu DR: Improving survival rate of Korean patients initiating dialysis. *Yonsei medical journal,* 56**:** 666-675, 2015.

29. van de Luijtgaarden MW, Jager KJ, Segelmark M, Pascual J, Collart F, Hemke AC, Remon C, Metcalfe W, Miguel A, Kramar R, Aasarod K, Abu Hanna A, Krediet RT, Schon S, Ravani P, Caskey FJ, Couchoud C, Palsson R, Wanner C, Finne P, Noordzij M: Trends in dialysis modality choice and related patient survival in the ERA-EDTA Registry over a 20-year period. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 2015.

30. Quinn RR, Hux JE, Oliver MJ, Austin PC, Tonelli M, Laupacis A: Selection bias explains apparent differential mortality between dialysis modalities. *Journal of the American Society of Nephrology : JASN*, 22**:** 1534-1542, 2011.

31. Weinhandl ED, Foley RN, Gilbertson DT, Arneson TJ, Snyder JJ, Collins AJ: Propensity-matched mortality comparison of incident hemodialysis and peritoneal dialysis patients. *Journal of the American Society of Nephrology : JASN*, 21**:** 499-506, 2010.

32. Mehrotra R, Chiu YW, Kalantar-Zadeh K, Vonesh E: The outcomes of continuous ambulatory and automated peritoneal dialysis are similar. *Kidney international*, 76**:** 97-107, 2009.

33. Nissenson AR, Prichard SS, Cheng IK, Gokal R, Kubota M, Maiorca R, Riella MC, Rottembourg J, Stewart JH: Non-medical factors that impact on ESRD modality selection. *Kidney international Supplement*, 40**:** S120-127, 1993.

34. Lameire N, Van Biesen W: Epidemiology of peritoneal dialysis: a story of believers and nonbelievers. *Nature reviews Nephrology*, 6**:** 75-82, 2010.

35. Liu FX, Gao X, Inglese G, Chuengsaman P, Pecoits-Filho R, Yu A: A Global Overview of the Impact of Peritoneal Dialysis First or Favored Policies: An Opinion. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis*, 35**:** 406-420, 2015.

36. Sedor JR, Watnick S, Patel UD, Cheung A, Harmon W, Himmelfarb J, Hostetter TH, Inrig JK, Mehrotra R, Robinson E, Smedberg PC, Shaffer RN: ASN End-Stage Renal Disease Task Force: perspective on prospective payments for renal dialysis facilities. *Journal of the American Society of Nephrology : JASN*, 21**:** 1235-1237, 2010.

37. Watnick S, Weiner DE, Shaffer R, Inrig J, Moe S, Mehrotra R: Comparing mandated health care reforms: the Affordable Care Act, accountable care organizations, and the Medicare ESRD program. *Clinical journal of the American Society of Nephrology : CJASN*, 7**:** 1535-1543, 2012.

38. Duong U, Kalantar-Zadeh K, Molnar MZ, Zaritsky JJ, Teitelbaum I, Kovesdy CP, Mehrotra R: Mortality associated with dose response of erythropoiesis-stimulating agents in hemodialysis versus peritoneal dialysis patients. *American journal of nephrology,* 35**:** 198-208, 2012.

39. Tantivess S, Werayingyong P, Chuengsaman P, Teerawattananon Y: Universal coverage of renal dialysis in Thailand: promise, progress, and prospects. *BMJ,* 346**:** f462, 2013.

40. Blake PG, Golper TA, Saxena AB: A critical shortage of solution threatens unprecedented growth in peritoneal dialysis. *Nephrology news & issues*, 28**:** 14-16, 2014.

41. Mehrotra R, Marsh D, Vonesh E, Peters V, Nissenson A: Patient education and access of ESRD patients to renal replacement therapies beyond in-center hemodialysis. *Kidney international,* 68**:** 378-390, 2005.

42. Kutner NG, Zhang R, Huang Y, Wasse H: Patient awareness and initiation of peritoneal dialysis. *Archives of internal medicine,* 171**:** 119-124, 2011.

43. Manns BJ, Taub K, Vanderstraeten C, Jones H, Mills C, Visser M, McLaughlin K: The impact of education on chronic kidney disease patients' plans to initiate dialysis with self-care dialysis: a randomized trial. *Kidney international,* 68**:** 1777-1783, 2005.

44. Lacson E, Jr., Wang W, DeVries C, Leste K, Hakim RM, Lazarus M, Pulliam J: Effects of a nationwide predialysis educational program on modality choice, vascular access, and patient outcomes. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 58**:** 235-242, 2011.

45. Schmidt RJ, Domico JR, Sorkin MI, Hobbs G: Early referral and its impact on emergent first dialyses, health care costs, and outcome. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 32**:** 278-283, 1998.

46. Lameire N, Van Biesen W: The pattern of referral of patients with end-stage renal disease to the nephrologist--a European survey. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 14 Suppl 6**:** 16-23, 1999.

47. Song JH, Kim GA, Lee SW, Kim MJ: Clinical outcomes of immediate full-volume exchange one year after peritoneal catheter implantation for CAPD. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 20**:** 194-199, 2000.

48. Banli O, Altun H, Oztemel A: Early start of CAPD with the Seldinger technique. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 25**:** 556-559, 2005.

49. Povlsen JV, Ivarsen P: How to start the late referred ESRD patient urgently on chronic APD. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 21 Suppl 2**:** ii56-59, 2006.

50. Jo YI, Shin SK, Lee JH, Song JO, Park JH: Immediate initiation of CAPD following percutaneous catheter placement without break-in procedure. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 27**:** 179-183, 2007.

51. Lobbedez T, Lecouf A, Ficheux M, Henri P, Hurault de Ligny B, Ryckelynck JP: Is rapid initiation of peritoneal dialysis feasible in unplanned dialysis patients? A single-centre experience. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 23**:** 3290-3294, 2008.

52. Yang YF, Wang HJ, Yeh CC, Lin HH, Huang CC: Early initiation of continuous ambulatory peritoneal dialysis in patients undergoing surgical implantation of Tenckhoff catheters. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 31**:** 551-557, 2011.

53. Ghaffari A: Urgent-start peritoneal dialysis: a quality improvement report. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 59**:** 400-408, 2012.

54. Koch M, Kohnle M, Trapp R, Haastert B, Rump LC, Aker S: Comparable outcome of acute unplanned peritoneal dialysis and haemodialysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 27**:** 375-380, 2012.

55. Alkatheeri AM, Blake P, Gray D, Jain A: Success of Urgent-Start Peritoneal Dialysis in a Large Canadian Renal Program. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 2015.

56. Mehrotra R: Expanding access to peritoneal dialysis for incident dialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 59**:** 330-332, 2012.

57. Oliver MJ, Garg AX, Blake PG, Johnson JF, Verrelli M, Zacharias JM, Pandeya S, Quinn RR: Impact of contraindications, barriers to self-care and support on incident peritoneal dialysis utilization. *Nephrology, dialysis, transplantation : official publication of the*

European Dialysis and Transplant Association - European Renal Association, 25**:** 2737-2744, 2010.

58. Cheng CH, Shu KH, Chuang YW, Huang ST, Chou MC, Chang HR: Clinical outcome of elderly peritoneal dialysis patients with assisted care in a single medical centre: a 25 year experience. *Nephrology (Carlton),* 18**:** 468-473, 2013.
59. Lobbedez T, Verger C, Ryckelynck JP, Fabre E, Evans D: Is assisted peritoneal dialysis associated with technique survival when competing events are considered? *Clinical journal of the American Society of Nephrology : CJASN,* 7**:** 612-618, 2012.
60. Bechade C, Lobbedez T, Ivarsen P, Povlsen JV: Assisted Peritoneal Dialysis for Older People with End-Stage Renal Disease: The French and Danish Experience. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 35**:** 663-666, 2015.
61. Oliver MJ, Quinn RR, Richardson EP, Kiss AJ, Lamping DL, Manns BJ: Home care assistance and the utilization of peritoneal dialysis. *Kidney international,* 71**:** 673-678, 2007.
62. Verger C, Duman M, Durand PY, Veniez G, Fabre E, Ryckelynck JP: Influence of autonomy and type of home assistance on the prevention of peritonitis in assisted automated peritoneal dialysis patients. An analysis of data from the French Language Peritoneal Dialysis Registry. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 22**:** 1218-1223, 2007.
63. Iyasere OU, Brown EA, Johansson L, Huson L, Smee J, Maxwell AP, Farrington K, Davenport A: Quality of Life and Physical Function in Older Patients on Dialysis: A Comparison of Assisted Peritoneal Dialysis with Hemodialysis. *Clinical journal of the American Society of Nephrology : CJASN*, 2015.

64. Mehrotra R, Soohoo M, Rivara MB, Himmelfarb J, Cheung AK, Arah OA, Nissenson AR, Ravel V, Streja E, Kuttykrishnan S, Katz R, Molnar MZ, Kalantar-Zadeh K: Racial and Ethnic Disparities in Use of and Outcomes with Home Dialysis in the United States. *Journal of the American Society of Nephrology : JASN*, 2015.

65. Brimble KS, Walker M, Margetts PJ, Kundhal KK, Rabbat CG: Meta-analysis: peritoneal membrane transport, mortality, and technique failure in peritoneal dialysis. *Journal of the American Society of Nephrology : JASN,* 17**:** 2591-2598, 2006.

66. Mehrotra R, Ravel V, Streja E, Kuttykrishnan S, Adams SV, Katz R, Molnar MZ, Kalantar-Zadeh K: Peritoneal Equilibration Test and Patient Outcomes. *Clinical journal of the American Society of Nephrology : CJASN,* 10**:** 1990-2001, 2015.

67. Devuyst O, Nielsen S, Cosyns JP, Smith BL, Agre P, Squifflet JP, Pouthier D, Goffin E: Aquaporin-1 and endothelial nitric oxide synthase expression in capillary endothelia of human peritoneum. *The American journal of physiology*, 275**:** H234-242, 1998.

68. Agre P: Aquaporin water channels (Nobel Lecture). *Angew Chem Int Ed Engl,* 43**:** 4278-4290, 2004.

69. Morelle J, Sow A, Vertommen D, Jamar F, Rippe B, Devuyst O: Quantification of osmotic water transport in vivo using fluorescent albumin. *American journal of physiology Renal physiology,* 307**:** F981-989, 2014.

70. Ni J, Verbavatz JM, Rippe A, Boisde I, Moulin P, Rippe B, Verkman AS, Devuyst O: Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis. *Kidney international,* 69**:** 1518-1525, 2006.

71. Rippe B, Stelin G, Haraldsson B: Computer simulations of peritoneal fluid transport in CAPD. *Kidney international,* 40**:** 315-325, 1991.

72. Stoenoiu MS, Ni J, Verkaeren C, Debaix H, Jonas JC, Lameire N, Verbavatz JM, Devuyst O: Corticosteroids induce expression of aquaporin-1 and increase transcellular

water transport in rat peritoneum. *Journal of the American Society of Nephrology : JASN,* 14**:** 555-565, 2003.

73. de Arteaga J, Ledesma F, Garay G, Chiurchiu C, de la Fuente J, Douthat W, Massari P, Terryn S, Devuyst O: High-dose steroid treatment increases free water transport in peritoneal dialysis patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 26**:** 4142-4145, 2011.
74. Yool AJ, Morelle J, Cnops Y, Verbavatz JM, Campbell EM, Beckett EA, Booker GW, Flynn G, Devuyst O: AqF026 is a pharmacologic agonist of the water channel aquaporin-1. *Journal of the American Society of Nephrology : JASN,* 24**:** 1045-1052, 2013.
75. Oh KH, Jung JY, Yoon MO, Song A, Lee H, Ro H, Hwang YH, Kim DK, Margetts P, Ahn C: Intra-peritoneal interleukin-6 system is a potent determinant of the baseline peritoneal solute transport in incident peritoneal dialysis patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 25**:** 1639-1646, 2010.
76. Pecoits-Filho R, Araujo MR, Lindholm B, Stenvinkel P, Abensur H, Romao JE, Jr., Marcondes M, De Oliveira AH, Noronha IL: Plasma and dialysate IL-6 and VEGF concentrations are associated with high peritoneal solute transport rate. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 17**:** 1480-1486, 2002.
77. Lambie M, Chess J, Donovan KL, Kim YL, Do JY, Lee HB, Noh H, Williams PF, Williams AJ, Davison S, Dorval M, Summers A, Williams JD, Bankart J, Davies SJ, Topley N: Independent effects of systemic and peritoneal inflammation on peritoneal dialysis survival. *Journal of the American Society of Nephrology : JASN,* 24**:** 2071-2080, 2013.

78. Rumpsfeld M, McDonald SP, Johnson DW: Higher peritoneal transport status is associated with higher mortality and technique failure in the Australian and New Zealand peritoneal dialysis patient populations. *Journal of the American Society of Nephrology : JASN*, 17**:** 271-278, 2006.

79. Gillerot G, Goffin E, Michel C, Evenepoel P, Biesen WV, Tintillier M, Stenvinkel P, Heimburger O, Lindholm B, Nordfors L, Robert A, Devuyst O: Genetic and clinical factors influence the baseline permeability of the peritoneal membrane. *Kidney international*, 67**:** 2477-2487, 2005.

80. Hwang YH, Son MJ, Yang J, Kim K, Chung W, Joo KW, Kim Y, Ahn C, Oh KH: Effects of interleukin-6 T15A single nucleotide polymorphism on baseline peritoneal solute transport rate in incident peritoneal dialysis patients. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis*, 29**:** 81-88, 2009.

81. Combet S, Van Landschoot M, Moulin P, Piech A, Verbavatz JM, Goffin E, Balligand JL, Lameire N, Devuyst O: Regulation of aquaporin-1 and nitric oxide synthase isoforms in a rat model of acute peritonitis. *Journal of the American Society of Nephrology : JASN*, 10**:** 2185-2196, 1999.

82. Ferrier ML, Combet S, van Landschoot M, Stoenoiu MS, Cnops Y, Lameire N, Devuyst O: Inhibition of nitric oxide synthase reverses changes in peritoneal permeability in a rat model of acute peritonitis. *Kidney international*, 60**:** 2343-2350, 2001.

83. Ni J, Moulin P, Gianello P, Feron O, Balligand JL, Devuyst O: Mice that lack endothelial nitric oxide synthase are protected against functional and structural modifications induced by acute peritonitis. *Journal of the American Society of Nephrology : JASN*, 14**:** 3205-3216, 2003.

84. Ni J, McLoughlin RM, Brodovitch A, Moulin P, Brouckaert P, Casadei B, Feron O, Topley N, Balligand JL, Devuyst O: Nitric oxide synthase isoforms play distinct roles

during acute peritonitis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 25**:** 86-96, 2010.

85. Devuyst O, Margetts PJ, Topley N: The pathophysiology of the peritoneal membrane. *Journal of the American Society of Nephrology : JASN,* 21**:** 1077-1085, 2010.
86. Morelle J, Sow A, Hautem N, Bouzin C, Crott R, Devuyst O, Goffin E: Interstitial Fibrosis Restricts Osmotic Water Transport in Encapsulating Peritoneal Sclerosis. *Journal of the American Society of Nephrology : JASN,* 26**:** 2521-2533, 2015.
87. Korte MR, Sampimon DE, Betjes MG, Krediet RT: Encapsulating peritoneal sclerosis: the state of affairs. *Nature reviews Nephrology,* 7**:** 528-538, 2011.
88. Lambie ML, John B, Mushahar L, Huckvale C, Davies SJ: The peritoneal osmotic conductance is low well before the diagnosis of encapsulating peritoneal sclerosis is made. *Kidney international,* 78**:** 611-618, 2010.
89. Sampimon DE, Barreto DL, Coester AM, Struijk DG, Krediet RT: The value of osmotic conductance and free water transport in the prediction of encapsulating peritoneal sclerosis. *Advances in peritoneal dialysis Conference on Peritoneal Dialysis,* 30**:** 21-26, 2014.
90. Williams JD, Craig KJ, Topley N, Von Ruhland C, Fallon M, Newman GR, Mackenzie RK, Williams GT: Morphologic changes in the peritoneal membrane of patients with renal disease. *Journal of the American Society of Nephrology : JASN,* 13**:** 470-479, 2002.
91. Yang AH, Chen JY, Lin JK: Myofibroblastic conversion of mesothelial cells. *Kidney international,* 63**:** 1530-1539, 2003.
92. Yanez-Mo M, Lara-Pezzi E, Selgas R, Ramirez-Huesca M, Dominguez-Jimenez C, Jimenez-Heffernan JA, Aguilera A, Sanchez-Tomero JA, Bajo MA, Alvarez V, Castro MA, del Peso G, Cirujeda A, Gamallo C, Sanchez-Madrid F, Lopez-Cabrera M: Peritoneal

dialysis and epithelial-to-mesenchymal transition of mesothelial cells. *The New England journal of medicine,* 348**:** 403-413, 2003.

93. Margetts PJ, Bonniaud P, Liu L, Hoff CM, Holmes CJ, West-Mays JA, Kelly MM: Transient overexpression of TGF-{beta}1 induces epithelial mesenchymal transition in the rodent peritoneum. *Journal of the American Society of Nephrology : JASN,* 16**:** 425-436, 2005.

94. Aroeira LS, Aguilera A, Selgas R, Ramirez-Huesca M, Perez-Lozano ML, Cirugeda A, Bajo MA, del Peso G, Sanchez-Tomero JA, Jimenez-Heffernan JA, Lopez-Cabrera M: Mesenchymal conversion of mesothelial cells as a mechanism responsible for high solute transport rate in peritoneal dialysis: role of vascular endothelial growth factor. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 46**:** 938-948, 2005.

95. Humphreys BD, Lin SL, Kobayashi A, Hudson TE, Nowlin BT, Bonventre JV, Valerius MT, McMahon AP, Duffield JS: Fate tracing reveals the pericyte and not epithelial origin of myofibroblasts in kidney fibrosis. *The American journal of pathology,* 176**:** 85-97, 2010.

96. Kriz W, Kaissling B, Le Hir M: Epithelial-mesenchymal transition (EMT) in kidney fibrosis: fact or fantasy? *The Journal of clinical investigation,* 121**:** 468-474, 2011.

97. Quaggin SE, Kapus A: Scar wars: mapping the fate of epithelial-mesenchymal-myofibroblast transition. *Kidney international,* 80**:** 41-50, 2011.

98. Chen YT, Chang YT, Pan SY, Chou YH, Chang FC, Yeh PY, Liu YH, Chiang WC, Chen YM, Wu KD, Tsai TJ, Duffield JS, Lin SL: Lineage tracing reveals distinctive fates for mesothelial cells and submesothelial fibroblasts during peritoneal injury. *Journal of the American Society of Nephrology : JASN,* 25**:** 2847-2858, 2014.

99. Garcia-Lopez E, Lindholm B, Davies S: An update on peritoneal dialysis solutions. *Nature reviews Nephrology,* 8**:** 224-233, 2012.

100. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, Jones B, Kulkarni H, Langham R, Ranganathan D, Schollum J, Suranyi MG, Tan SH, Voss D: The effect of low glucose degradation product, neutral pH versus standard peritoneal dialysis solutions on peritoneal membrane function: the balANZ trial. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 27**:** 4445-4453, 2012.

101. Johnson DW, Dent H, Hawley CM, McDonald SP, Rosman JB, Brown FG, Bannister K, Wiggins KJ: Association of dialysis modality and cardiovascular mortality in incident dialysis patients. *Clinical journal of the American Society of Nephrology : CJASN,* 4**:** 1620-1628, 2009.

102. Isoyama N, Machowska A, Qureshi AR, Yamamoto T, Anderstam B, Heimburger O, Barany P, Stenvinkel P, Lindholm B: Elevated Circulating S100a12 Associates with Vascular Disease and Worse Clinical Outcome in Peritoneal Dialysis Patients. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 2015.

103. Boudville N, Kemp A, Clayton P, Lim W, Badve SV, Hawley CM, McDonald SP, Wiggins KJ, Bannister KM, Brown FG, Johnson DW: Recent peritonitis associates with mortality among patients treated with peritoneal dialysis. *Journal of the American Society of Nephrology : JASN,* 23**:** 1398-1405, 2012.

104. Davies SJ, Phillips L, Griffiths AM, Russell LH, Naish PF, Russell GI: What really happens to people on long-term peritoneal dialysis? *Kidney international,* 54**:** 2207-2217, 1998.

105. Kim H, Kim KH, Ahn SV, Kang SW, Yoo TH, Ahn HS, Hann HJ, Lee S, Ryu JH, Yu M, Kim SJ, Kang DH, Choi KB, Ryu DR: Risk of major cardiovascular events among

incident dialysis patients: A Korean national population-based study. *International journal of cardiology,* 198**:** 95-101, 2015.

106. Wang AY, Brimble KS, Brunier G, Holt SG, Jha V, Johnson DW, Kang SW, Kooman JP, Lambie M, McIntyre C, Mehrotra R, Pecoits-Filho R: ISPD Cardiovascular and Metabolic Guidelines in Adult Peritoneal Dialysis Patients Part I - Assessment and Management of Various Cardiovascular Risk Factors. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 35**:** 379-387, 2015.
107. Wang AY, Brimble KS, Brunier G, Holt SG, Jha V, Johnson DW, Kang SW, Kooman JP, Lambie M, McIntyre C, Mehrotra R, Pecoits-Filho R: ISPD Cardiovascular and Metabolic Guidelines in Adult Peritoneal Dialysis Patients Part II - Management of Various Cardiovascular Complications. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 35**:** 388-396, 2015.
108. Little J, Phillips L, Russell L, Griffiths A, Russell GI, Davies SJ: Longitudinal lipid profiles on CAPD: their relationship to weight gain, comorbidity, and dialysis factors. *Journal of the American Society of Nephrology : JASN,* 9**:** 1931-1939, 1998.
109. Attman PO, Samuelsson OG, Moberly J, Johansson AC, Ljungman S, Weiss LG, Knight-Gibson C, Alaupovic P: Apolipoprotein B-containing lipoproteins in renal failure: the relation to mode of dialysis. *Kidney international,* 55**:** 1536-1542, 1999.
110. de Moraes TP, Fortes PC, Ribeiro SC, Riella MC, Pecoits-Filho R: Comparative analysis of lipid and glucose metabolism biomarkers in non-diabetic hemodialysis and peritoneal dialysis patients. *Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia,* 33**:** 173-179, 2011.
111. Johnson DW, Armstrong K, Campbell SB, Mudge DW, Hawley CM, Coombes JS, Prins JB, Isbel NM: Metabolic syndrome in severe chronic kidney disease: Prevalence,

predictors, prognostic significance and effects of risk factor modification. *Nephrology (Carlton),* 12**:** 391-398, 2007.

112. Jiang N, Qian J, Lin A, Lindholm B, Axelsson J, Yao Q: Initiation of glucose-based peritoneal dialysis is associated with increased prevalence of metabolic syndrome in non-diabetic patients with end-stage renal disease. *Blood purification,* 26**:** 423-428, 2008.

113. Szeto CC, Chow KM, Kwan BC, Chung KY, Leung CB, Li PK: New-onset hyperglycemia in nondiabetic chinese patients started on peritoneal dialysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 49**:** 524-532, 2007.

114. Choi SJ, Kim NR, Hong SA, Lee WB, Park MY, Kim JK, Hwang SD, Lee HK: Changes in body fat mass in patients after starting peritoneal dialysis. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 31**:** 67-73, 2011.

115. Lievense H, Kalantar-Zadeh K, Lukowsky LR, Molnar MZ, Duong U, Nissenson A, Krishnan M, Krediet R, Mehrotra R: Relationship of body size and initial dialysis modality on subsequent transplantation, mortality and weight gain of ESRD patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 27**:** 3631-3638, 2012.

116. Ahmadi SF, Zahmatkesh G, Streja E, Mehrotra R, Rhee CM, Kovesdy CP, Gillen DL, Ahmadi E, Fonarow GC, Kalantar-Zadeh K: Association of Body Mass Index with Mortality in Peritoneal Dialysis Patients: A Systematic Review and Meta-Analysis. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis*, 2015.

117. Bergstrom J, Furst P, Alvestrand A, Lindholm B: Protein and energy intake, nitrogen balance and nitrogen losses in patients treated with continuous ambulatory peritoneal dialysis. *Kidney international,* 44**:** 1048-1057, 1993.

118. Park J, Ahmadi SF, Streja E, Molnar MZ, Flegal KM, Gillen D, Kovesdy CP, Kalantar-Zadeh K: Obesity paradox in end-stage kidney disease patients. *Progress in cardiovascular diseases,* 56**:** 415-425, 2014.

119. McDonald SP, Collins JF, Johnson DW: Obesity is associated with worse peritoneal dialysis outcomes in the Australia and New Zealand patient populations. *Journal of the American Society of Nephrology : JASN,* 14**:** 2894-2901, 2003.

120. Fernandes NM, Bastos MG, Franco MR, Chaoubah A, Lima Mda G, Divino-Filho JC, Qureshi AR: Body size and longitudinal body weight changes do not increase mortality in incident peritoneal dialysis patients of the Brazilian peritoneal dialysis multicenter study. *Clinics (Sao Paulo),* 68**:** 51-58, 2013.

121. Badve SV, Paul SK, Klein K, Clayton PA, Hawley CM, Brown FG, Boudville N, Polkinghorne KR, McDonald SP, Johnson DW: The association between body mass index and mortality in incident dialysis patients. *PloS one,* 9**:** e114897, 2014.

122. Liao CT, Kao TW, Chou YH, Wu MS, Chen YM, Chuang HF, Hung KY, Chu TS, Wu KD, Tsai TJ: Associations of metabolic syndrome and its components with cardiovascular outcomes among non-diabetic patients undergoing maintenance peritoneal dialysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 26**:** 4047-4054, 2011.

123. Szeto CC, Kwan BC, Chow KM, Leung CB, Cheng MS, Law MC, Li PK: Metabolic syndrome in peritoneal dialysis patients: choice of diagnostic criteria and prognostic implications. *Clinical journal of the American Society of Nephrology : CJASN,* 9**:** 779-787, 2014.

124. Chou CY, Liang CC, Kuo HL, Chang CT, Liu JH, Lin HH, Wang IK, Yang YF, Huang CC: Comparing risk of new onset diabetes mellitus in chronic kidney disease patients receiving peritoneal dialysis and hemodialysis using propensity score matching. *PloS one,* 9**:** e87891, 2014.

125. Woodward RS, Schnitzler MA, Baty J, Lowell JA, Lopez-Rocafort L, Haider S, Woodworth TG, Brennan DC: Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons,* 3**:** 590-598, 2003.

126. Davies SJ, Woodrow G, Donovan K, Plum J, Williams P, Johansson AC, Bosselmann HP, Heimburger O, Simonsen O, Davenport A, Tranaeus A, Divino Filho JC: Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *Journal of the American Society of Nephrology : JASN,* 14**:** 2338-2344, 2003.

127. Wolfson M, Piraino B, Hamburger RJ, Morton AR: A randomized controlled trial to evaluate the efficacy and safety of icodextrin in peritoneal dialysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 40**:** 1055-1065, 2002.

128. de Moraes TP, Andreoli MC, Canziani ME, da Silva DR, Caramori JC, Ponce D, Cassi HV, de Andrade Bastos K, Rio DR, Pinto SW, Filho SR, de Campos LG, Olandoski M, Divino-Filho JC, Pecoits-Filho R: Icodextrin reduces insulin resistance in non-diabetic patients undergoing automated peritoneal dialysis: results of a randomized controlled trial (STARCH). *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 30**:** 1905-1911, 2015.

129. Paniagua R, Ventura MD, Avila-Diaz M, Cisneros A, Vicente-Martinez M, Furlong MD, Garcia-Gonzalez Z, Villanueva D, Orihuela O, Prado-Uribe MD, Alcantara G, Amato D: Icodextrin improves metabolic and fluid management in high and high-average transport diabetic patients. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 29**:** 422-432, 2009.

130. Li PK, Culleton BF, Ariza A, Do JY, Johnson DW, Sanabria M, Shockley TR, Story K, Vatazin A, Verrelli M, Yu AW, Bargman JM: Randomized, controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. *Journal of the American Society of Nephrology : JASN,* 24**:** 1889-1900, 2013.

131. Sniderman AD, Sloand JA, Li PK, Story K, Bargman JM: Influence of low-glucose peritoneal dialysis on serum lipids and apolipoproteins in the IMPENDIA/EDEN trials. *Journal of clinical lipidology,* 8**:** 441-447, 2014.

132. Duong U, Mehrotra R, Molnar MZ, Noori N, Kovesdy CP, Nissenson AR, Kalantar-Zadeh K: Glycemic control and survival in peritoneal dialysis patients with diabetes mellitus. *Clinical journal of the American Society of Nephrology : CJASN,* 6**:** 1041-1048, 2011.

133. Yoo DE, Park JT, Oh HJ, Kim SJ, Lee MJ, Shin DH, Han SH, Yoo TH, Choi KH, Kang SW: Good glycemic control is associated with better survival in diabetic patients on peritoneal dialysis: a prospective observational study. *PloS one,* 7**:** e30072, 2012.

134. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Nigwekar SU, Hegbrant J, Strippoli GF: HMG CoA reductase inhibitors (statins) for dialysis patients. *The Cochrane database of systematic reviews,* 9**:** CD004289, 2013.

135. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk

V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet,* 377**:** 2181-2192, 2011.

136. Bargman JM, Thorpe KE, Churchill DN: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *Journal of the American Society of Nephrology : JASN,* 12**:** 2158-2162, 2001.

137. Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT: Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Journal of the American Society of Nephrology : JASN,* 15**:** 1061-1070, 2004.

138. Fernandez-Lucas M, Teruel-Briones JL, Gomis-Couto A, Villacorta-Perez J, Quereda-Rodriguez-Navarro C: Maintaining residual renal function in patients on haemodialysis: 5-year experience using a progressively increasing dialysis regimen. *Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia,* 32**:** 767-776, 2012.

139. Lin YF, Huang JW, Wu MS, Chu TS, Lin SL, Chen YM, Tsai TJ, Wu KD: Comparison of residual renal function in patients undergoing twice-weekly versus three-times-weekly haemodialysis. *Nephrology (Carlton),* 14**:** 59-64, 2009.

140. Seo EY, An SH, Cho JH, Suh HS, Park SH, Gwak H, Kim YL, Ha H: Effect of biocompatible peritoneal dialysis solution on residual renal function: a systematic review

of randomized controlled trials. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 34**:** 724-731, 2014.

141. Kjaergaard KD, Peters CD, Jespersen B, Tietze IN, Madsen JK, Pedersen BB, Novosel MK, Laursen KS, Bibby BM, Strandhave C, Jensen JD: Angiotensin blockade and progressive loss of kidney function in hemodialysis patients: a randomized controlled trial. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 64**:** 892-901, 2014.

142. Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT: Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney international,* 62**:** 1046-1053, 2002.

143. Moist LM, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA, Hulbert-Shearon T, Jones CA, Bloembergen WE: Predictors of loss of residual renal function among new dialysis patients. *Journal of the American Society of Nephrology : JASN,* 11**:** 556-564, 2000.

144. van Biesen W, Claes K, Covic A, Fan S, Lichodziejewska-Niemierko M, Schoder V, Verger C, Wabel P: A multicentric, international matched pair analysis of body composition in peritoneal dialysis versus haemodialysis patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 28**:** 2620-2628, 2013.

145. Ha IS, Yap HK, Munarriz RL, Zambrano PH, Flynn JT, Bilge I, Szczepanska M, Lai WM, Antonio ZL, Gulati A, Hooman N, van Hoeck K, Higuita LM, Verrina E, Klaus G, Fischbach M, Riyami MA, Sahpazova E, Sander A, Warady BA, Schaefer F: Risk factors for loss of residual renal function in children treated with chronic peritoneal dialysis. *Kidney international,* 88**:** 605-613, 2015.

146. Medcalf JF, Harris KP, Walls J: Role of diuretics in the preservation of residual renal function in patients on continuous ambulatory peritoneal dialysis. *Kidney international,* 59**:** 1128-1133, 2001.

147. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, Jones B, Kulkarni H, Langham R, Ranganathan D, Schollum J, Suranyi M, Tan SH, Voss D: Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. *Journal of the American Society of Nephrology : JASN,* 23**:** 1097-1107, 2012.

148. Cho Y, Johnson DW, Craig JC, Strippoli GF, Badve SV, Wiggins KJ: Biocompatible dialysis fluids for peritoneal dialysis. *The Cochrane database of systematic reviews,* 3**:** CD007554, 2014.

149. Udayaraj UP, Steenkamp R, Caskey FJ, Rogers C, Nitsch D, Ansell D, Tomson CR: Blood pressure and mortality risk on peritoneal dialysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 53**:** 70-78, 2009.

150. Davies SJ, Davenport A: The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. *Kidney international,* 86**:** 489-496, 2014.

151. Brown EA, Davies SJ, Rutherford P, Meeus F, Borras M, Riegel W, Divino Filho JC, Vonesh E, van Bree M: Survival of functionally anuric patients on automated peritoneal dialysis: the European APD Outcome Study. *Journal of the American Society of Nephrology : JASN,* 14**:** 2948-2957, 2003.

152. Jansen MA, Termorshuizen F, Korevaar JC, Dekker FW, Boeschoten E, Krediet RT: Predictors of survival in anuric peritoneal dialysis patients. *Kidney international,* 68**:** 1199-1205, 2005.

153. Johnson DW, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Badve SV: Superior survival of high transporters treated with automated

versus continuous ambulatory peritoneal dialysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 25**:** 1973-1979, 2010.

154. Cho Y, Johnson DW, Badve S, Craig JC, Strippoli GF, Wiggins KJ: Impact of icodextrin on clinical outcomes in peritoneal dialysis: a systematic review of randomized controlled trials. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 28**:** 1899-1907, 2013.

155. Mehrotra R, Duong U, Jiwakanon S, Kovesdy CP, Moran J, Kopple JD, Kalantar-Zadeh K: Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 58**:** 418-428, 2011.

156. John B, Tan BK, Dainty S, Spanel P, Smith D, Davies SJ: Plasma volume, albumin, and fluid status in peritoneal dialysis patients. *Clinical journal of the American Society of Nephrology : CJASN,* 5**:** 1463-1470, 2010.

157. Tan BK, Yu Z, Fang W, Lin A, Ni Z, Qian J, Woodrow G, Jenkins SB, Wilkie ME, Davies SJ: Longitudinal bioimpedance vector plots add little value to fluid management of peritoneal dialysis patients. *Kidney international,* 2015.

158. Cho Y, Johnson DW: Peritoneal dialysis-related peritonitis: towards improving evidence, practices, and outcomes. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 64**:** 278-289, 2014.

159. Johnson DW, Dent H, Hawley CM, McDonald SP, Rosman JB, Brown FG, Bannister KM, Wiggins KJ: Associations of dialysis modality and infectious mortality in incident dialysis patients in Australia and New Zealand. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 53**:** 290-297, 2009.

160. Szeto CC, Wong TY, Chow KM, Leung CB, Li PK: The clinical course of culture-negative peritonitis complicating peritoneal dialysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 42**:** 567-574, 2003.

161. Szeto CC, Chow KM, Kwan BC, Law MC, Chung KY, Yu S, Leung CB, Li PK: Staphylococcus aureus peritonitis complicates peritoneal dialysis: review of 245 consecutive cases. *Clinical journal of the American Society of Nephrology : CJASN,* 2**:** 245-251, 2007.

162. Szeto CC, Kwan BC, Chow KM, Lau MF, Law MC, Chung KY, Leung CB, Li PK: Coagulase negative staphylococcal peritonitis in peritoneal dialysis patients: review of 232 consecutive cases. *Clinical journal of the American Society of Nephrology : CJASN,* 3**:** 91-97, 2008.

163. Barraclough K, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Johnson DW: Corynebacterium peritonitis in Australian peritoneal dialysis patients: predictors, treatment and outcomes in 82 cases. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 24**:** 3834-3839, 2009.

164. Fahim M, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Johnson DW: Culture-negative peritonitis in peritoneal dialysis patients in Australia: predictors, treatment, and outcomes in 435 cases. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 55**:** 690-697, 2010.

165. Miles R, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Johnson DW: Predictors and outcomes of fungal peritonitis in peritoneal dialysis patients. *Kidney international,* 76**:** 622-628, 2009.

166. Barraclough K, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Johnson DW: Polymicrobial peritonitis in peritoneal dialysis patients in

Australia: predictors, treatment, and outcomes. *American journal of kidney diseases : the official journal of the National Kidney Foundation*, 55**:** 121-131, 2010.

167. Edey M, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Johnson DW: Enterococcal peritonitis in Australian peritoneal dialysis patients: predictors, treatment and outcomes in 116 cases. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 25**:** 1272-1278, 2010.

168. Fahim M, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Johnson DW: Coagulase-negative staphylococcal peritonitis in Australian peritoneal dialysis patients: predictors, treatment and outcomes in 936 cases. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 25**:** 3386-3392, 2010.

169. Govindarajulu S, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Johnson DW: Staphylococcus aureus peritonitis in Australian peritoneal dialysis patients: predictors, treatment, and outcomes in 503 cases. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis*, 30**:** 311-319, 2010.

170. Jarvis EM, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Johnson DW: Predictors, treatment, and outcomes of non-Pseudomonas Gram-negative peritonitis. *Kidney international*, 78**:** 408-414, 2010.

171. Ghali JR, Bannister KM, Brown FG, Rosman JB, Wiggins KJ, Johnson DW, McDonald SP: Microbiology and outcomes of peritonitis in Australian peritoneal dialysis patients. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis*, 31**:** 651-662, 2011.

172. Brown MC, Simpson K, Kerssens JJ, Mactier RA: Encapsulating peritoneal sclerosis in the new millennium: a national cohort study. *Clinical journal of the American Society of Nephrology : CJASN*, 4**:** 1222-1229, 2009.

173. Johnson DW, Cho Y, Livingston BE, Hawley CM, McDonald SP, Brown FG, Rosman JB, Bannister KM, Wiggins KJ: Encapsulating peritoneal sclerosis: incidence, predictors, and outcomes. *Kidney international,* 77**:** 904-912, 2010.

174. Howard K, Hayes A, Cho Y, Cass A, Clarke M, Johnson DW: Economic evaluation of neutral-pH, low-glucose degradation product peritoneal dialysis solutions compared with standard solutions: a secondary analysis of the balANZ Trial. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 65**:** 773-779, 2015.

175. Morton RL, Snelling P, Webster AC, Rose J, Masterson R, Johnson DW, Howard K: Dialysis modality preference of patients with CKD and family caregivers: a discrete-choice study. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 60**:** 102-111, 2012.

176. Campbell DJ, Johnson DW, Mudge DW, Gallagher MP, Craig JC: Prevention of peritoneal dialysis-related infections. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 30**:** 1461-1472, 2015.

177. Huang JW, Hung KY, Yen CJ, Wu KD, Tsai TJ: Comparison of infectious complications in peritoneal dialysis patients using either a twin-bag system or automated peritoneal dialysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 16**:** 604-607, 2001.

178. Han SH, Lee SC, Ahn SV, Lee JE, Choi HY, Kim BS, Kang SW, Choi KH, Han DS, Lee HY: Improving outcome of CAPD: twenty-five years' experience in a single Korean

center. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 27**:** 432-440, 2007.

179. Moraes TP, Pecoits-Filho R, Ribeiro SC, Rigo M, Silva MM, Teixeira PS, Pasqual DD, Fuerbringer R, Riella MC: Peritoneal dialysis in Brazil: twenty-five years of experience in a single center. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 29**:** 492-498, 2009.

180. Huang ST, Chuang YW, Cheng CH, Wu MJ, Chen CH, Yu TM, Shu KH: Evolution of microbiological trends and treatment outcomes in peritoneal dialysis-related peritonitis. *Clinical nephrology*, 75**:** 416-425, 2011.

181. Rocha A, Rodrigues A, Teixeira L, Carvalho MJ, Mendonca D, Cabrita A: Temporal trends in peritonitis rates, microbiology and outcomes: the major clinical complication of peritoneal dialysis. *Blood purification,* 33**:** 284-291, 2012.

182. Ozisik L, Ozdemir FN, Tanriover MD: The changing trends of peritoneal dialysis related peritonitis and novel risk factors. *Renal failure,* 37**:** 1027-1032, 2015.

183. Kiernan L, Kliger A, Gorban-Brennan N, Juergensen P, Tesin D, Vonesh E, Finkelstein F: Comparison of continuous ambulatory peritoneal dialysis-related infections with different "Y-tubing" exchange systems. *Journal of the American Society of Nephrology : JASN,* 5**:** 1835-1838, 1995.

184. Lo WK, Chan CY, Cheng SW, Poon JF, Chan DT, Cheng IK: A prospective randomized control study of oral nystatin prophylaxis for Candida peritonitis complicating continuous ambulatory peritoneal dialysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 28**:** 549-552, 1996.

185. Thodis E, Bhaskaran S, Pasadakis P, Bargman JM, Vas SI, Oreopoulos DG: Decrease in Staphylococcus aureus exit-site infections and peritonitis in CAPD patients by local

application of mupirocin ointment at the catheter exit site. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 18**:** 261-270, 1998.

186. Bernardini J, Bender F, Florio T, Sloand J, Palmmontalbano L, Fried L, Piraino B: Randomized, double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis patients. *Journal of the American Society of Nephrology : JASN,* 16**:** 539-545, 2005.

187. Troidle L, Finkelstein F: Treatment and outcome of CPD-associated peritonitis. *Annals of clinical microbiology and antimicrobials,* 5**:** 6, 2006.

188. Gadola L, Poggi C, Poggio M, Saez L, Ferrari A, Romero J, Fumero S, Ghelfi G, Chifflet L, Borges PL: Using a multidisciplinary training program to reduce peritonitis in peritoneal dialysis patients. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 33**:** 38-45, 2013.

189. Zhang L, Hawley CM, Johnson DW: Focus on peritonea dialysis training: working to decrease peritonitis rates. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association***:** in press, 2015.

190. Schaepe C, Bergjan M: Educational interventions in peritoneal dialysis: a narrative review of the literature. *International journal of nursing studies,* 52**:** 882-898, 2015.

191. ANZDATA Registry: 37th Report, Chapter 5: Peritoneal Dialysis, Australia and New Zealand Dialysis and Transplant Registry. Adelaide, Australia, 2015.

192. Jose MD, Johnson DW, Mudge DW, Tranaeus A, Voss D, Walker R, Bannister KM: Peritoneal dialysis practice in Australia and New Zealand: a call to action. *Nephrology (Carlton),* 16**:** 19-29, 2011.

193. Johnson DW, Badve SV, Pascoe EM, Beller E, Cass A, Clark C, de Zoysa J, Isbel NM, McTaggart S, Morrish AT, Playford EG, Scaria A, Snelling P, Vergara LA, Hawley CM:

Antibacterial honey for the prevention of peritoneal-dialysis-related infections (HONEYPOT): a randomised trial. *The Lancet Infectious diseases,* 14**:** 23-30, 2014.

194. Campbell DJ, Brown F, Craig J, Gallagher M, Johnson DW, Kirkland G, Kumar SK, Lim WH, Ranganathan D, Saweirs W, Sud K, Toussaint ND, Walker RG, Yehia M, Mudge DW: Assessment of current practice and barriers to antimicrobial prophylaxis in peritoneal dialysis patients. *Nephrology (Carlton),* 19**:** 42, 2014.

195. Walker A, Bannister K, George C, Mudge D, Yehia M, Lonergan M, Chow J: KHA-CARI Guideline: peritonitis treatment and prophylaxis. *Nephrology (Carlton),* 19**:** 69-71, 2014.

196. Zhang L, Badve SV, Pascoe EM, Beller E, Cass A, Clark C, De Zoysa J, Isbel NM, McTaggart S, Morrish AT, Playford EG, Scaria A, Snelling P, Vergara LA, Hawley CM, Johnson DW, Honeypot Study Collaborative: Microbiological results of the HONEYPOT study - secondary analysis of a randomised, controlled trial of exit site application of medihoney for the prevention of catheter-associated infections in PD patients. . *Nephrology (Carlton),* 19**:** 30, 2014.

197. Piraino B, Bernardini J, Brown E, Figueiredo A, Johnson DW, Lye WC, Price V, Ramalakshmi S, Szeto CC: ISPD position statement on reducing the risks of peritoneal dialysis-related infections. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 31**:** 614-630, 2011.

198. Kopriva-Altfahrt G, Konig P, Mundle M, Prischl F, Roob JM, Wiesholzer M, Vychytil A, Arneitz K, Karner A, Artes R, Wolf E, Auinger M, Pawlak A, Fraberger J, Hofbauer S, Galvan G, Salmhofer H, Pichler B, Wazel M, Gruber M, Thonhofer A, Hager A, Malajner S, Heiss S, Braunsteiner T, Zweiffler M, Rudnicki M, Kogler R, Kohlhauser D, Wiesinger T, Moser E, Kotanko P, Loibner H, Nitz H, Miska HJ, Wenzel R, Wolfer M, Breuss H, Holzl B, Prischi F, Schmekal B, Riener EM, Wonisch W, Vikydal R, Frank B, Wieser C,

Pokorny K: Exit-site care in Austrian peritoneal dialysis centers -- a nationwide survey. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 29**:** 330-339, 2009.

199. Kavanagh D, Prescott GJ, Mactier RA: Peritoneal dialysis-associated peritonitis in Scotland (1999-2002). *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 19**:** 2584-2591, 2004.

200. Davenport A: Peritonitis remains the major clinical complication of peritoneal dialysis: the London, UK, peritonitis audit 2002-2003. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 29**:** 297-302, 2009.

201. Martin LC, Caramori JC, Fernandes N, Divino-Filho JC, Pecoits-Filho R, Barretti P: Geographic and educational factors and risk of the first peritonitis episode in Brazilian Peritoneal Dialysis study (BRAZPD) patients. *Clinical journal of the American Society of Nephrology : CJASN,* 6**:** 1944-1951, 2011.

202. Figueiredo AE, Moraes TP, Bernardini J, Poli-de-Figueiredo CE, Barretti P, Olandoski M, Pecoits-Filho R: Impact of patient training patterns on peritonitis rates in a large national cohort study. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 30**:** 137-142, 2015.

203. Badve SV, Smith A, Hawley CM, Johnson DW: Adherence to guideline recommendations for infection prophylaxis in peritoneal dialysis patients. *NDT plus,* 2**:** 508, 2009.

204. Nadeau-Fredette AC, Johnson DW, Hawley CM, Pascoe E, Cho Y, Clayton PA, Borlace M, Badve SV, Sud K, Boudville N, McDonald SP: Centre-specific factors associated with

peritonitis risk - a multi-center registry analysis. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis***:** in press, 2015.

205. Jose M, Johnson DW, Mudge DW, Tranaeus A, Voss D, Walker R, Bannister KM: Peritoneal dialysis practice in Australia and New Zealand: A call to action. *Nephrology,* 16**:** 19-29, 2011.

206. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, Johnson DW, Kuijper EJ, Lye WC, Salzer W, Schaefer F, Struijk DG: Peritoneal dialysis-related infections recommendations: 2010 update. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* 30**:** 393-423, 2010.

Figure Legends

Figure 1: Major landmarks in the development of peritoneal dialysis as a treatment for end-stage renal disease (1923-'78). Abbreviations, AKI: acute kidney injury; PD, peritoneal dialysis.

Figure 2: Secular trends in the number of patients treated with peritoneal dialysis in the United States (1996-2013). (1A) The number of patients treated with peritoneal dialysis by 90 of start of maintenance dialysis; (1B) Point prevalent counts of the number of patients treated with peritoneal dialysis as of December 31 of each calendar year.

Figure 3: Secular trends in the proportion of patients undergoing maintenance dialysis treated with peritoneal dialysis in the United States (1996-2013). The blue line represents the proportion of all patients undergoing maintenance dialysis treated with peritoneal dialysis 90 days from the date of first dialysis and the red line represents the proportion of all patients undergoing maintenance dialysis on December 31 of any calendar year.

Figure 4: Overview of interrelationships between modality-specific factors that may contribute to the cardiovascular risk of patients undergoing peritoneal dialysis

Figure 5: Center-specific PD-related peritonitis rates (incidence rate ratios) in Australia during the periods 2004-2008 (open triangles) and 2009-2013 (solid circles)

Table 1: Summary of studies from around the world demonstrating greater reductions in risk for death in patients treated with peritoneal dialysis compared to in-center hemodialysis

Author, Publication Year	Country/Region	Eras	Mortality Trends by Modality	Trends in comparative survival
Mehrotra, '07[22]	United States	1996-1997 1998-1999 2000-2001 2002-2003	Compared to 1998-1999, the adjusted hazards for patients starting peritoneal dialysis to die or transfer to hemodialysis within 12 months was 17% lower; no significant difference over time for patients starting hemodialysis	
Mehrotra, '11[23]	United States	1996-1998 1999-2001 2002-2004		The adjusted hazards ratio for death (PD/HD) were 1.07 (1.04, 1.11), 1.08 (1.06-1.11), and 1.03 (0.99, 1.06) respectively
Chang, '12[24]	Taiwan	1997-2001 2002-2006		The adjusted hazards ratio for death (PD/HD) were 1.33 (1.21, 1.46), and 0.99 (0.87, 1.14) respectively
Yeates, '12[25]	Canada	1991-1995 1996-2000 2001-2004		The adjusted hazards ratio for death (PD/HD) were 1.08 (1.02, 1.15), 1.13 (1.07, 1.20), and 0.99 (0.92, 1.06), respectively
Heaf, '14[26]	Denmark	1990-1994 1995-1999	Adjusted death risk for patients starting hemodialysis and peritoneal dialysis in 2005-2010	The adjusted hazards ratio for death (PD/HD) were 0.95 (0.85, 1.06), 0.90 (0.82, 1.00), 0.84

		2000-2004 2005-2010	was 30% (95% confidence interval, 13-37%) and 46% (95% confidence interval, 37-51%) lower compared to patients who started hemodialysis in 1990-1994	(0.77, 0.92), and 0.80 (0.71, 0.89), respectively
Marshall, '15[27]	Australia and New Zealand	1998-2002 2003-2007 2008-2012	Compared to 1998-2002, adjusted death risk for patients starting hemodialysis in 2008-2012 was 21% lower (95% confidence interval, 15-26%) compared to 1998-2002; for patients starting PD, 27% lower (95% confidence interval, 11-23%)	
Ryu, '15[28]	South Korea	Each year, from 2005 through 2008	Compared to 2005, in 2008 adjusted death risk for patients starting hemodialysis was 15% lower (95% confidence interval, 9-20%) and starting peritoneal dialysis 25% lower (95% confidence interval, 16-34%)	Among patients who started dialysis in 2008, no significant difference in risk for death for patients treated with HD, compared to those treated with PD (adjusted hazards ratio, 0.91 (0.82, 1.00))
van de Luijtgaarden, '15[29]	Europe (ERA-EDTA Registry)	1993-1997 1998-2002 2003-2007	Compared to 1993-1997, adjusted death risk for patients starting hemodialysis in 2003-2007 was 18% lower (95% confidence interval 16-20%) and starting peritoneal dialysis was 36% lower (95% confidence interval, 33-39%)	The adjusted hazards ratio for death (PD/HD) were 1.02 (0.98, 1.06), 1.00 (0.96, 1.03), and 0.91 (0.88, 0.95), respectively

Table 2: Important thematic areas in need for further research

Utilization and Outcomes with Peritoneal Dialysis

- Approaches to modality education that optimize decision support and reduce decisional conflict
- Clinical outcomes of late-referred patients starting treatment with PD ("urgent-start" PD) and in-center hemodialysis with central venous catheter
- Comparative effectiveness of home and in-center dialysis for end-of-life care for patients with end-stage renal disease
- Understanding reasons for the low utilization of PD by racial/ethnic minorities and tailored interventions to overcome barriers
- Adequately powered studies comparing a broad range of patient-reported outcomes with different dialysis modalities, including effect-modification by cultural differences

Peritoneal Physiology and Pathobiology

- Mechanisms of osmosis, choice of solutions, new osmotic agents, combination of different types of osmotic agents
- Biomarkers of peritoneal solute and water transfer - at baseline and over time on PD: genetics, proteomics, metabolomics
- Nanoparticles, new indications for PD: intoxications (liposome supported peritoneal dialysis for intoxication and metabolic disorders
- Getting hematopoietic stem cells from patients on PD
- Identification of other molecular counterparts of additional transport structures, e.g. the small pores

Cardiovascular Risk with Peritoneal Dialysis

- Validation of more practical approach to defining metabolic syndrome for PD patients

- Better understanding of high risk cardiovascular risk phenotypes to include interactions with diabetes, gender and ethnicity
- Adequately powered study to test the benefit of statins
- Trials to evaluate additional strategies for preserving residual kidney function
- Trials addressing the risk/benefit of preserving residual kidney function while optimizing volume status and blood pressure management, including further evaluation of technologies to evaluate fluid status at the bedside.

Peritonitis

- Determining which PD training methods, curricula and structured assessment methods lead to better peritonitis rates
- Determining whether structured periodic retraining after initial baseline training leads to a reduction in peritonitis rates
- Development and evaluation of rapid (within hours) organism identification methods in PD-related peritonitis.
- Does use of continuous vs. intermittent intraperitoneal antibiotics for peritonitis treatment lead to better peritonitis outcomes?
- Does temporary conversion of automated PD patients to continuous ambulatory PD during peritonitis treatment lead to better outcomes compared with leaving patients on automated PD?